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10/522966

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 29 JUL 2004

WIPO

PCT

Applicant's or agent's file reference RCS/PF4905		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/08386	International filing date (day/month/year) 29.07.2003	Priority date (day/month/year) 31.07.2002	
International Patent Classification (IPC) or both national classification and IPC C07D401.04			
Applicant SMITHKLINE BEECHAM CORPORATION et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.



☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

EPO - DG 1

27. 08. 2004

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 28.01.2004	Date of completion of this report 28.07.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931 

**INTERNATIONAL PRELIMINARY
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International application No. **PCT/EP 03/08386**

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-27 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,10 (all part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,10 (all part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	1-15
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item I

Basis of the opinion

The application is directed to

- (i) 4-(3-phenyl-pyrid-4-yl)-5-(phenyl or pyridyl)-triazoles (I) (claims 1-10),
- (ii) a pharmaceutical composition comprising compounds (I) (claim 11),
- (iii) the second medical use of compounds (I) (claims 12-14), and
- (iv) the first medical use of compounds (I) (claim 15).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The ISA has not issued a search report for the claims 1 and 10, insofar as the expression derivative is concerned (cf. search report). No International Preliminary Examination has thus been carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 Reference is made to the following documents.

- D1: WO-A-02066462, 29.08.2002.
- D2: WO-A-03042211, 22.05.2003.
- D3: Revesz, L. *et al. Biorg. Med. Chem. Lett.* (19-08-2002), 12(16), 2109-2112.
- D4: WO-A-0240476, 23.05.2002.
- D5: WO-A-0178723, 25.10.2001.
- D6: WO-A-9958128, 18.11.1999.

The documents D1 to D3 were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

- 2 Novelty

2.1 **D4** relates to pyridyl substituted triazoles as inhibitors of the TGF-beta signalling pathway. The present compounds (I) differ from the compounds of D4 through the 4-(3-phenyl-pyrid-4-yl) substituent (corresponding to the phenyl, naphthyl, or fused phenyl R¹ substituent of the compounds of D4). The present claimed matter is thus novel in view of D4.

D5 discloses triazole derivatives as type 2 methionine aminopeptidase inhibitors. The present compounds (I) differ from the compounds of D5 through the 4-(3-phenyl-pyrid-4-yl) substituent (corresponding to R³ of the compounds of D5). The present claimed matter is thus novel in view of D5.

D6 relates to pyridyl substituted imidazoles as inhibitors of the TGF-beta type I receptor. The present compounds (I) differ from the compounds of D6 in being triazoles rather than imidazoles (cf. D6, drawings 7-9). The present claimed matter is thus novel in view of D6.

In view of D4-D6 the application complies with the criterion of novelty.

2.2 **D1** relates to pyrazole derivatives as inhibitors of the TGF-beta signalling pathway. The compounds of D1 are substituted by 2-pyridyl and 3-phenyl-pyrid-4-yl groups alike the present compounds (I) (cf. claims 3 and 7), and the present compounds (I) differ from those of D1 merely in being triazoles rather than pyrazoles. The document is thus not relevant to the question of novelty of the present application. It may, however, become relevant to the question of inventive step in the regional phase if the present claimed priority could not be acknowledged.

D2 relates to phenyl substituted triazoles as inhibitors of the TGF-beta signalling pathway. The present compounds (I) differ from the compounds of D2 through the 4-(3-phenyl-pyrid-4-yl) substituent (corresponding to the phenyl, naphthyl, or fused phenyl R¹ substituent of the compounds of D2). The document is thus not relevant to the question of novelty of the present application.

D3 relates to p38 MAP kinase inhibitors. In this context the document discloses 4-(4-pyridyl)-5-(4-fluorophenyl)-triazole from which the present compounds (I) differ through the additional phenyl substituent at the pyridyl group. The document is thus not relevant to the question of novelty of the present application.

3 Inventive Step

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- 3.1 The application describes the synthesis of certain compounds (I) and reports that all the examples represent modulators of the activin-like kinase 5 receptor (synonymous with Alk5 receptor and TGF-beta type I receptor) and show TGF-beta cellular activity (cf. the application, page 27). Due to these effects the compounds are believed to be useful e.g. in the treatment of the diseases of claim 13.
- 3.2 At present D4 is considered to represent the most relevant state of the art, because it relates already to pyridyl substituted triazoles of the desired activity. Starting from D4 the problem underlying the present application may be seen in the provision of further inhibitors of the TGF-beta signalling pathway, and in particular in the provision of inhibitors of the Alk5 receptor. Considering only the documents D4 to D6 (rather than document D1), the present claimed compounds do not appear obvious, because the said documents do not hint or suggest that triazoles with the present 4-(3-phenyl-pyrid-4-yl) substituent would retain the desired activity. Consequently the claims 1-15 appear to meet the requirements of inventive step.
- 4 The present set of claims does not comply with the requirements of Article 6 PCT for the following reasons.
- 4.1 Claims 1 and 10 are directed to compounds (I) and derivatives thereof. Thus, the claims also embrace compounds i.e. derivatives having structures and formulae different from those compounds represented by formula (I). The claims, however, do not give any clear indication to the structure or formulae of such derivatives. Neither from the description nor from the claims it is apparent which structural features found in formula (I) must necessarily be present in said derivatives, and which structural features may be varied. Therefore, claims 1 and 10 embrace compounds different from formula (I) without clearly defining the structure or formulae of such derivatives. Consequently, the scope of claims 1 and 10 is not clear, contrary to the requirements of Article 6 PCT.
- 4.2 With regard to the second medical use claim 12 the EPO would raise an objection if the therapeutic application was functionally defined by a mechanism of action, because such definition does not allow any practical application in the form of a defined, real treatment of a pathological condition. Such objection may be avoided by either introducing in the claims a list of pathological conditions cited in the application, or by showing that means are available which would allow the skilled person to recognize which additional conditions would fall within the functional

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definition.

5 Further Deficiencies of the Application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D4 to D6 is not mentioned in the description, nor are these documents identified therein.